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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,011	10/23/2000	Feng Yan	1889-34	8985

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06/18/2002

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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 06/18/2002

5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/694,011

Applicant(s)

YAN ET AL.

Examiner

Shahnam Sharareh

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 April 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-75 is/are pending in the application.
- 4a) Of the above claim(s) 27-33,35,36,38-40 and 47-75 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25,26,34,37 and 41-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 27-33,35,36,38-40 and 47-75 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1.5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 25-46 in Paper No. 3 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant's elections of air as gas A, C₄F₁₀ as gas B and phosphatidic acid as the phospholipid are also acknowledged. Claims 25-26, 34, 37, 41-46 read on the elected species.
2. Claims 47-75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 3. Claims 27-33, 35-36, 38-40 are further withdrawn as they are not directed to the elected species.
3. This application contains claims 47-75 drawn to an invention nonelected with traverse in Paper No. 3. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

- An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).
- When claiming priority,

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

In the instant case, the U.S. application Serial No. 09/021,367, now US Patent 6,183,725 filed on February 10, 1998 and any of its parent cases do not meet the requirement of the first paragraph of 35 USC 112 with respect to the methods of preparing contrast agent for ultrasound imaging using C₄F₁₀, Air and phosphatidic acid as the elemental components.

Examiner points out that "specific claims to single compounds require reasonably specific supporting disclosure; while naming is not essential, something more than disclosure of class of 100,000 or even 48 compounds is required; given time, a chemist could name all of the half million compounds within scope of broadest claim, which claims is supported by broad disclosure, this does not constitute support for each compound individually when separately claimed." *In re Ruschig*, 154 USPQ 118, CCPA

1967. Accordingly, species within a genus must be sufficiently disclosed in the parent cases. In the instant case, although some of the broad claims may have support to earlier filed priority applications, the invention as a whole (i.e., including limitations set forth in dependent claims) is given the effective priority date of October 23, 2000 which is the filing date of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 25-26, 34, 37, 41-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First, Applicant is informed that the requirement under 35 USC §112, first paragraph, for "written description of the invention" is separate and distinct from the requirement for enablement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use" or simply disclose an element of a claimed invention; rather, the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. MPEP 2163.05 (I).

Although one might not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that the

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inventor invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989), MPEP 2163.02. "Thus, a specification may enable one skilled in the art to make and use an invention and yet not describe the invention." *Vas-Cath Inc, v. Mahurkar*, 953 F.2d at 1562-63. In addition, species within a genus must be sufficiently disclosed to provide for the written description requirement under 112 first paragraph. *In re Ruschig*. Accordingly, the test for written description requirement considers the disclosure of the application and whether it reasonably conveys to the artisan that the inventor had possession of the invention as the whole, including the claimed species, at that time of the application was filed. Here, the possession of the invention as a whole is assessed based on such methods employing the combined the elected species, namely the use of C_4F_{10} as gas B, air as gas A and phosphatidic acid as the phospholipid in preparing ultrasound contrast agents.

6. In the instant case, the application teaches a broad general process that can be considered in a general sense to teach how to make ultrasound agents once a desired final product is determined to be made. However, nowhere in the instant specification nor the instant examples is there any mention of preparing an ultrasound contrast agent using the elected species of C_4F_{10} , air and phosphatidic acid. Accordingly, the description requirements are not satisfied as the disclosure of the application does not reasonably convey to an artisan that the inventor had possession of the application at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 25-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "usual" in claim 25 is a relative term which renders the claim indefinite. The term "usual" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 25-26, 34, 37, 41-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US

Patent 5,597,549, claims 1-12 of US Patent 5,445,813, claims 11-13 of US Patent 5,271,928, claims 10-16 of US Patent 5,643,553. Although the conflicting claims are not identical, they are not patentably distinct from each other because all sets of claims are drawn methods of preparing an ultrasound contrast agent using a specific perfluorocarbon gas in combination with a secondary gas such as air and a surfactant such as dipalmitoylphosphatidic acid which would be encompassed within the broader claims of the cited patent. Moreover, the cited patents are all directed to ultrasound contrast agents, accordingly, the pending claims are obvious variants of the patented claims because it would have been obvious to one of ordinary skill in the art at the time of invention that both sets of claims are essentially the same.

7. Claims 25-26, 34, 37, 41-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 09/748,120, claims 16, 34-36, 44, 71-72; copending Application No. 09/770216, claims 35-36; copending Application No. 09/401,836 claims 18-25; copending Application No. 09/401,835, claims 4-9; copending Application No. 09/736,361, claims 11-22. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to the use of ultrasound contrast agents comprising the same sub-genus of perfluorocarbons as the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.\

9. Claims 25-26, 34, 37, 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger US Patent 5,205,290.

The instant claims are directed to a methods of preparing pharmaceutically acceptable contrast agent comprising microbubble comprising perfluorobutane gas and air.

Unger discloses methods of preparing contrast imaging agents comprising volatile liquids useful in heating expansion selected from the group of perfluorocarbons such as those having between 1 and about 9 carbon atoms, especially C₄F₁₀ (perfluorobutane) (col 4, lines 25-29) in combination with a gas such as air (col 5, lines 15-18; claims 6-8). The contrast agents of Unger comprising gaseous microspheres having expanding compounds within the microspheres of the contrast agents and a gas (see abstract, col 4, lines 9-58). Unger's contrast agents are heated prior to use to allow expansion of the internal gas thus, there exists two sets of gases within the microspheres of Unger (see col 4, lines 49-55). Unger discloses the use of liquids which undergo liquid/gas transition (see col 4, line 59-61).

Unger further discloses microspheres comprising volatile perfluorobutane (col 9, lines 65-68) which by its nature undergoes liquid/gas transition. As the claimed

components of Unger are the same as those instantly claimed; namely gas A, gas B and the surfactant, the minimum effective proportion of the at least perfluorobutane component of Unger's compositions, during their liquid/gas transition time, would inherently follow the instantly claimed criteria. Accordingly, Unger anticipates the limitations of the instant contrast agents.

10. Claims 25-26, 34, 37, 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Schutt et al US Patent 5,639,443.

Schutt discloses methods of preparing ultrasound contrast agents comprising a first gas such as air and a second osmotic gas such as perfluorobutane surrounded by a membrane such as a phospholipid surfactant (see abstract; col 3, lines 40-67; col 12, line 17-20; col 15, lines 44-63; col 16, lines 56-65; examples III-VI; claims 1-23). Since the components of Schutt's microbubbles are the same as those instantly claimed; namely gas A, gas B and the surfactant, the minimum effective proportion of the perfluorobutane component of Schutt's microbubbles would inherently follow the instantly claimed criteria. Accordingly, Schutt anticipates the limitations of the instant contrast agents.

11. Claims 25-26, 34, 37, 41-42, 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Lohrmann US Patent 5,562,893.

Lohrmann discloses methods of preparing gaseous ultrasonic contrast agent comprising a phospholipid wall optionally attached to a non-ionic hydrophilic moiety such as polyethylene glycol and at least one gas or mixtures of gases such as perfluorobutane and air (see abstract, col 4, lines 1-64; col 7, lines 16-55, table II;

claims 14-18). Since the components of Lohrmann's microspheres are the same as those instantly claimed; namely gas A, gas B and the surfactant, the minimum effective proportion of the perfluorobutane component of Lohrmann's microspheres would inherently follow the instantly claimed criteria. Accordingly, Lohrmann anticipates the limitations of the instant contrast agents.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 25-26, 34, 37, 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schutt in view of Unger US Patent 5,585,112.

Schutt's teachings are described above. Schutt primarily teaches the use of two types of gases in ultrasonic microbubble containing contrast agents. Schutt lacks the specific use of surfactants containing phosphatidic acids.

Unger teaches ultrasonic contrast agents comprising liposomes containing perfluorobutane and dipalmitoylphosphatidic acid coated with PEG. Unger does not teach the combination of two types of gases in his liposomes.

The teachings of Schutt and Unger are analogous because they both teach the use of gaseous microbubbles in the field of ultrasound imaging.

13. Even though Schutt does not teach the use of phosphatidic acid in his microbubbles, he teaches the use of phospholipids as a suitable gas encapsulating moiety, thus, it would have been obvious to one of ordinary skill in the art at the time of invention to any suitable phospholipid such as phosphatidic acid, because as taught by Unger, the ordinary skill in the art would have had a reasonable expectation of success in formulating stable gas carrying liposomes suitable for ultrasound imaging.

14. "The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, the combined

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teachings of Schutt and Unger renders the instant claims obvious, because use of gaseous mixtures and phosphatidic acid in preparing ultrasound imaging agents flow naturally from the suggestion of the prior art.


Conclusion

15. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, JD can be reached on 703-308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

ss
June 11, 2002


RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200